# Mediator and cell cycle regulation

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## ABSTRACT

The multiprotein Mediator complex is an evolutionarily conserved coregulator of eukaryotic transcription. Mediator functions as a bridge between gene-specific transcription factors and the RNA polymerase II transcription machinery. Mutations affecting Mediator function have been associated with a large number of diseases from cancer to neurodegenerative disorders. In the present thesis we address how Mediator affects cell cycle progression using the fission yeast *Schizosaccharomyces pombe* as a model.

The Cyclin dependent kinase 8 (Cdk8) and its partner Cyclin C (CycC) are both components of Mediator. The Cdk8-CycC pair is recruited together with Mediator to genes periodically transcribed during cell cycle progression. Deletion of Cdk8 or inactivation of the Cdk8 associated kinase activity results in delayed mitotic entry and delayed activation of mitotic genes. An important target for the Cdk8 kinase activity is Fkh2, a gene specific transcription activator required for periodic transcription of mitotic genes in fission yeast. Fkh2 mutations that abolish Cdk8-phosphorylation delay mitotic progression, whereas mutations that mimic protein phosphorylation cause early entry into mitosis.

Cdk8 activity is regulated by two other Mediator components, Med12 and Med13, which connect the Cdk8-CycC pair to the core Mediator. Loss of Med12 and Med13 leads to the formation of a free pool of Cdk8 that can stimulate early entry into mitosis, i.e. an effect directly opposite to that observed upon loss of kinase activity.

In our work, we have also investigated the link between cell cycle progression and transcription. We report that transcription of periodically expressed genes relies solely on the activity of the master cell cycle regulator, Cdk1, independent of the current stage of cell cycle progression.

In conclusion, our observations firmly establish Mediator as a regulator of mitotic progression in fission yeast. Our work also provides a framework of ideas that may be explored to better understand how mutations affecting Mediator function in human cells may lead to disturbed cell cycle control and the development of cancer.

**Keywords**: mediator, cell cycle, cdk8, fission yeast, cancer

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This thesis is based on the following studies:

**I.** **Cyclin-dependent kinase 8 regulates mitotic commitment in fission yeast.**
Szilagyi Z, Banyai G, Lopez MD, McInerny CJ, Gustafsson CM.
*Mol Cell Biol. 2012 Jun;32(11):2099-109.*

**II.** **Mediator can regulate mitotic entry and direct periodic transcription in fission yeast.**
Banyai G, Lopez MD, Szilagyi Z, Gustafsson CM.
*Mol Cell Biol. 2014 Nov;34(21):4008-18.*

**III.** **Cyclin C influences the timing of mitosis in fission yeast.**
Banyai G, Szilagyi Z, Baraznenok V, Khorosjutina O, Holmberg S, Gustafsson CM.
*MANUSCRIPT*

**IV.** **Cdk1 activity acts as a quantitative platform for coordinating cell cycle progression with periodic transcription.**
Banyai G, Baidi F, Coudreuse D, Szilagyi Z.
*MANUSCRIPT (submitted)*

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